

PATENT. ATTORNEY DÖCKET NO. 00398

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Alan S. Kopin et al.

Art Unit:

Not Assigned

Serial No.:

09/966,871

Examiner:

Not Assigned

Filed:

September 28, 2001

Customer No.:

21559

Title:

ASSAYS FOR IDENTIFYING RECEPTORS HAVING

ALTERATIONS IN SIGNALING

Assistant Commissioner For Patents Washington, DC 20231

RECEIVED

MAY 0 8 2002

TECH CENTER 1600/2900

## INFORMATION DISCLOSURE STATEMENT

Applicant submits the references listed on the attached form PTO-1449, copies of which are enclosed.

Submission of this statement is not a representation that a search has been made, nor is information included in this statement an admission that the information is material to patentability.

This statement is being filed before the receipt of a first Office action on the merits.

Please apply any charges or credits to Deposit Account 03-2095.

Respectfully submitted,

Date:

10 garay 200Z

aren L. Elbing, Ph.D.

Reg. No. 35,238

Clark & Elbing LLP 176 Federal Street Boston, MA 02110

Telephone: 617-428-0200 Facsimile: 617-428-7045

F:\00398\00398.512002 IDS.wpd

21559 PATENT TRADEMARK OFFICE

RECEIVED

MAY O 8 2002

TECH CENTER 1600/2900

EXAMINER	DATE CONSIDERED

receptor ligands" J. Biol. Chem. 269:11687-11690 (1994)

Barker et al., "Constitutively active 5-hydroxytryptamine<sub>2C</sub> receptors reveal novel inverse agonist activity of

		Sheet <u>2</u> of <u>6</u>
SUBSTITUTE FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE	Attorney Docket No.	00398/512002
(MODIFIED) PATENT AND TRADEMARK OFFICE	Serial No.	09/966,871
	Applicant	Alan S. Kopin et al.
INFORMATION DISCLOSURE	Filing Date	September 28, 2001
STATEMENT BY APPLICANT (Use several sheets if necessary)	Group	Not Assigned May
	IDS Filed	January 2002
(37 C.F.R. §1.98(b))	Customer No.	21559 CENTRA
Beinborn et al., "A single amino acid of the cholecystokinin- peptide antagonists" <i>Nature</i> 362:348-350 (1993)	B/gastrin receptor deter	O9/966,871  Alan S. Kopin et al.  September 28, 2001  Not Assigned  January 2002  21559  Traines specificity for non-
Black et al., "Inverse agonists exposed" Nature 374:214-21	5 (1995)	
Blevins et al., "Characterization of cholecystokinin <sub>a</sub> receptor agonist activity by a family of cholecystok receptor agonists" <i>J. Pharmacol. Exp. Ther.</i> 269:911-916 (1994)		mily of cholecystokinin <sub>B</sub>
Bond et al., "Physiological effects of inverse agonists in train β <sub>2</sub> -adrenoceptor" <i>Nature</i> 374:272-276 (1995)	nsgenic mice with myoc	ardial overexpression of the
Chang et al., "A potent nonpeptide cholecystokinin antagon Aspergillus Alliaceus" Science 230:177-179 (1985)	ist selective for peripher	ral tissues isolated from
Chen et al., "Molecular cloning and functional expression of Pharmacology 44:8-12 (1993)	a μ-opioid receptor fror	n rat brain" <i>Molecular</i>
Chen et al., "Physiological disposition and metabolism of L-cholecystokinin receptor, in laboratory animals" <i>Drug Metab</i>		
Chu et al., "Effect of endogenous hypergastrinemia on gast transplanted to athymic rats" Gastroenterology 109:1415-14		human colon carcinoma
Clapham, "Mutations in G protein-linked receptors: novel in:	sights on disease" Cell 7	75:1237-1239 (1993)
Coughlin, "Expanding horizons for receptors coupled to G p Cell Biology 6:191-197 (1994)	roteins: diversity and dis	sease" Current Opinion in
DeLean et al., "A ternary complex model explains the agonic cyclase-coupled β-adrenergic receptor" J. Biol. Chem. 255:		erties of the adenylate
		· · · · · · · · · · · · · · · · · · ·

 Asperginus Amateus Science 250.111-119 (1905)
Chen et al., "Molecular cloning and functional expression of a μ-opioid receptor from rat brain" Molecular Pharmacology 44:8-12 (1993)
Chen et al., "Physiological disposition and metabolism of L-365,260, a potent antagonist of brain cholecystokinin receptor, in laboratory animals" <i>Drug Metabolism and Disposition</i> 20:390-395 (1992)
Chu et al., "Effect of endogenous hypergastrinemia on gastrin receptor expressing human colon carcinoma transplanted to athymic rats" <i>Gastroenterology</i> 109:1415-1420 (1995)
Clapham, "Mutations in G protein-linked receptors: novel insights on disease" Cell 75:1237-1239 (1993)
 Coughlin, "Expanding horizons for receptors coupled to G proteins: diversity and disease" Current Opinion in Cell Biology 6:191-197 (1994)
DeLean et al., "A ternary complex model explains the agonist-specific binding properties of the adenylate cyclase-coupled β-adrenergic receptor" <i>J. Biol. Chem.</i> 255:7108-7117 (1980)
Dethloff et al., "Cholecystokinin antagonists - a toxicologic perspective" Drug Metabolism Reviews 24:267-296 (1992)
Ding et al., "Cholecystokinin-B receptor ligands of the dipeptoid series act as agonists on rat stomach histidine decarboxylase" <i>Gastroenterology</i> 109:1181-1187 (1995)
Dourish et al., "Postponement of satiety by blockade of brain cholecystokinin (CCK-B) receptors" Science 245:1509-1511 (1989)
Evans et al., "Design of potent, orally effective, nonpeptidal antagonists of the peptide hormone cholecystokinin" <i>Proc. Natl. Acad. Sci. USA</i> 83:4918-4922 (1986)
Guidobono et al., "Stress related changes in calcitonin gene-related peptide binding sites in the cat central nervous system" <i>Neuropeptides</i> 91:57-63 (1991)
 Harro et al., "CCK in animal and human research on anxiety" Trends Pharmacol. Sci. 14:244-249 (1993)

EXAMINER	DATE CONSIDERED
EVANABLED, Initial station considered. Describes the contribution	Alon if well in conference and well according to the last

Sheet <u>3</u> of <u>6</u>

SUBSTITUTE FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE (MODIFIED) PATENT AND TRADEMARK OFFICE	Attorney Docket No.	00398/512002
(MODIFIED) - FATENT AND TRADEMARK OFFICE	Serial No.	09/966,871
	Applicant	Alan S. Kopin et al.
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	September 25, 2001
(Use several sheets if necessary)	Group	Not Assigned 2003
	IDS Filed	January 11, 2002
(37 C.F.R. §1.98(b))	Customer No.	21559

	Hausdorff et al., "A mutation of the β <sub>2</sub> -adrenergic receptor impairs agonist activation of adenylyl cyclase without affecting high affinity agonist binding" <i>J. Biol. Chem.</i> 265:1388-1393 (1990)
	Heinflink et al., "A constitutively active mutant thyrotropin-releasing hormone receptor is chronically down-regulated in pituitary cells: evidence using chlordiazepoxide as a negative antagonist" <i>Molecular Endocrinology</i> 9:1455-1460 (1995)
	Henke et al., "3-(1 <i>H</i> -Indazol-3-ylmethyl)-1,5-benzodiazepines: CCK-A agonists that demonstrate oral activity as satiety agents" <i>J. Med. Chem.</i> 39:2655-2658 (1996)
	Höcker et al., "PD 135158, a CCK <sub>B</sub> /gastrin receptor agonists, stimulates rat pancreatic enzyme secretion as a CCK <sub>A</sub> receptor agonist" Eur. J. Pharmacol. 242:105-108 (1993)
	Högger et al., "Activating and inactivating mutations in N- and C-terminal i3 loop junctions of muscarinic acetylcholine Hm1 receptors" <i>J. Biol. Chem.</i> 270:7405-7410 (1995)
, "	Horwell, "Development of CCK-B antagonists" Neuropeptides 19(Suppl.):57-64 (1991)
	Horwell, "Peptoid approaches in the design of antagonists of substance P and cholecystokinin" Eur. J. Med. Chem. 30 Suppl. 537s-550s (1995)
	Horwell et al., "Rationally designed 'dipeptoid' analogues of CCK. α-methyltryptophan derivatives as highly selective and orally active gastrin and CCK-B antagonists with potent anxiolytic properties" <i>J. Med. Chem.</i> 34:404-414 (1991)
	Ishizuka et al., "The effect of gastrin on growth of human stomach cancer cells" Ann. Surg. 215:528-535 (1992)
	Jackson, "Structure and function of G protein coupled receptors" Pharmacol. Ther. 50:425-442 (1991)
	Kenakin, "On the definition of efficacy. Antagonists may possess negative efficacy" <i>Trends Pharmacol. Sci.</i> 15:408-409 (1994)
	Kjelsberg et al., "Constitutive activation on the α <sub>18</sub> -adrenergic receptor by all amino acid substitutions at a single site. Evidence for a region which constrains receptor activation" <i>J. Biol Chem.</i> 267:1430-1433 (1992)
	Koop et al., "A new CCK-B/gastrin receptor antagonist acts as an agonist on the rat pancreas" <i>Digestion</i> 54:286-287 (1993)
	Kopin et al., "The role of the cholecystokinin-B/gastrin receptor transmembrane domains in determining affinity for subtype-selective ligands" <i>J. Biol. Chem.</i> 270:5019-5023 (1995)
	Kopin et al., "Expression cloning and characterization of the canine parietal cell gastrin receptor" <i>Proc. Natl. Acad. Sci. USA</i> 89:3605-3609 (1992)
	Kopp et al., "Brief report: congenital hyperthyroidism caused by a mutation in the thyrotropin-receptor gene" N. Engl. J. Med. 332:150-154 (1995)
	Latronico et al., "A novel mutation of the luteinizing hormone receptor gene causing male gonadotropin-independent precocious puberty" J. Clin. Endocrinol. Metab. 80:2490-2494 (1995)

EXAMINER	DATE CONSIDERED
EVALUATED LIVE A REAL PROPERTY OF THE PROPERTY	

Sheet <u>4</u> of <u>6</u>

SUBSTITUTE FORM PTO-1449 U.S. DEPARTMENT OF COMMER (MODIFIED) PATENT AND TRADEMARK OFFI		00398/512002
(MODIFIED) PATENT AND TRADEMARK OFFI	Serial No.	09/966,871
	Applicant	Alan S. Kopin et al.
INFORMATION DISCLOSURE	Filing Date	September 28, 2001
STATEMENT BY APPLICANT (Use several sheets if necessary)	Group	Not Assigned
	IDS Filed	January 11, 28021
(37 C.F.R. §1.98(b))	Customer No.	21559

 <u> </u>
Lazareno et al., "Estimation of antagonist K <sub>b</sub> from inhibition curves in functional experiments: alternatives to the Cheng-Prusoff equation" <i>Trends Pharmacol. Sci.</i> 14:237-239 (1993)
Lee et al., "The human brain cholecystokinin-B/Gastrin Receptor" J. Biol. Chem. 268:8164-8169 (1993)
Leff, "The two-state model of receptor activation" Trends Pharmacol. Sci. 14:303-307 (1993)
Lefkowitz, "Constitutive activity of receptors coupled to guanine nucleotide regulatory proteins" <i>Trends Pharmacol. Sci.</i> 14:303-304 (1993)
Lefkowitz, "Turned on to ill effect" Nature 365:603-607 (1993)
Lloyd et al., "Peripheral regulation of gastric acid secretion" in <i>Physiology of the Gastrointestinal Tract</i> 1185-1226, Raven Press, New York (1994)
Lotti et al., "A new potent and selective non-peptide gastrin antagonist and brain cholecystokinin receptor (CCK-B) ligand L-365,260" Eur. J. Pharmacol. 162:273-280 (1989)
Matus-Leibovitch et al., "Truncation of the thyrotropin-releasing hormone receptor carboxyl tail causes constitutive activity and leads to impaired responsiveness in <i>xenopus</i> oocytes and AtT20 cells" <i>J. Biol Chem.</i> 270:1041-1047 (1995)
McPherson, "Analysis of radioligand binding experiments. A collection of computer programs for the IBM PC" <i>J. Pharmacol. Meth.</i> 14:213-228 (1985)
Milligan et al., "Inverse agonism: pharmacological curiosity or potential therapeutic strategy?" Trends Pharamcol. Sci. 16:10-13 (1995)
Nishida et al., "Pharmacological profile of (R)-1-[2,3-dihydro-1-(2'-methyl-phenacyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3-methylphenyl)urea (YM022), a new potent and selective gastrin/cholecystokinin-B receptor antagonist, in Vitro and in Vivo" J. Pharmacol. Exp. Ther. 269:725-731 (1994)
Nishida et al., "YM022 {(R)-1-[2,3-dihydro-1-(2'-methylphenacyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3-methylphenyl)urea}, a potent and selective gastrin/cholecystokinin-B receptor antagonist, prevents gastric and duodenal lesions in rats" <i>J. Pharmacol. Exp. Ther.</i> 270:1256-1261 (1994)
Parker et al., "Truncation of the extended carboxyl-terminal domain increases the expression and regulatory activity of the Avian β-adrenergic receptor" <i>J. Biol. Chem.</i> 266:9987-9996 (1991)
Parma et al., "Constitutively active receptors as a disease-causing mechanism" Molec. Cell Endocrinol. 100:159-162 (1994)
Parma et al., "Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas" Nature 365:649-651 (1993)
Parma et al., "Somatic mutations causing constitutive activity of the thyrotropin receptor are the major cause of hyperfunctioning thyroid adenomas: identification of additional mutations activating both the cyclic adenosine 3', 5'-monophosphate and inositol phosphate-Ca <sup>2+</sup> Cascades" <i>Molecular Endocrinology</i> 9:725-733 (1995)

EXAMINER	DATE CONSIDERED

		Sheet <u>5</u> of <u>6</u>
SUBSTITUTE FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE (MODIFIED) PATENT AND TRADEMARK OFFICE	Attorney Docket No.	00398/512002
	Serial No.	09/966,871
	Applicant	Alan S. Kopin et al.
INFORMATION DISCLOSURE	Filing Date	September 28, 2001
STATEMENT BY APPLICANT (Use several sheets if necessary)	Group	00398/512002 09/966,871 Alan S. Kopin et al. September 28, 2001 Not Assigned January 11, 2002 21559  utations causing constitutive
	IDS Filed	January 11, 2002
(37 C.F.R. §1.98(b))	Customer No.	21559
Paschke et al., "Identification and functional characterization activation of the thyrotropin receptor in hyperfunctioning au <i>Endocrinol. Metab.</i> 79:1785-1789 (1994)	n of two new somatic m tonomous adenomas of	utations causing constitutive the thyroid" <i>J. Clin.</i>
Patchett et al., "Design and biological activities of L-163,19 secretagogue" <i>Proc. Natl. Acad. Sci. USA</i> 92:7001-7005 (1		orally active growth hormone
Patel et al., "Biological properties of the benzodiazepine and B/gastrin receptor antagonist with high affinity in Vitro and 146:943-948 (1994)		
Pei et al., "A constitutively active mutant β₂-adrenergic rece phosphorylated" <i>Proc. Natl. Acad. Sci. USA</i> 91:2699-2702		sensitized and
Perlman et al., "Non-peptide angiotensin agonist" J. Biol. C.	hem. 270:1493-1496 (19	995)
Pfeiffer et al., "Muscarinic M2-receptors enhance polyphosp FEBS Letters 204:352-356 (1986)	phoinositol release in rat	gastric mucosal cells"
Porcellini et al., "Somatic mutations in the VI transmembrar activate cAMP signalling in thyroid hyperfunctioning adenor		
Rao et al., "Rhodopsin mutation G90D and a molecular med 367:639-641 (1994)	chanism for congenitcal	night blindness" Nature
Ren et al., "Constitutively active mutants of the α <sub>2</sub> -adrenerg	ic receptor" J. Biol.Cher.	n. 268:16483-16487 (1993)
Robbins et al., "Pigmentation phenotypes of variant extensi MSH receptor function" Cell 72:827-834 (1993)	on locus alleles result fr	om point mutations that alter
Robinson et al., "Constitutively active mutants of rhodopsin	" Neuron 9:719-725 (199	92)
Sakamoto et al., "Distinct subdomains of human endothelin selective antagonist and endotheling-selective agonists" J. a.	receptors determine the Biol. Chem. 268:8547-85	eir selectivity to endothelin <sub>A</sub> -

 F
Perlman et al., "Non-peptide angiotensin agonist" J. Biol. Chem. 270:1493-1496 (1995)
Pfeiffer et al., "Muscarinic M2-receptors enhance polyphosphoinositol release in rat gastric mucosal cells" FEBS Letters 204:352-356 (1986)
Porcellini et al., "Somatic mutations in the VI transmembrane segment of the thyrotropin receptor constitutively activate cAMP signalling in thyroid hyperfunctioning adenomas" <i>Oncogene</i> 11:1089-1093 (1995)
Rao et al., "Rhodopsin mutation G90D and a molecular mechanism for congenitcal night blindness" <i>Nature</i> 367:639-641 (1994)
Ren et al., "Constitutively active mutants of the α <sub>2</sub> -adrenergic receptor" J. Biol.Chem. 268:16483-16487 (1993)
 Robbins et al., "Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function" Cell 72:827-834 (1993)
Robinson et al., "Constitutively active mutants of rhodopsin" Neuron 9:719-725 (1992)
Sakamoto et al., "Distinct subdomains of human endothelin receptors determine their selectivity to endothelin <sub>A</sub> -selective antagonist and endothelin <sub>B</sub> -selective agonists" <i>J. Biol. Chem.</i> 268:8547-8553 (1993)
Samama et al., "A mutation-induced activated state of the $\beta_2$ -adrenergic receptor" <i>J. Biol. Chem.</i> 268:4625-4635 (1993)
 Samama et al., "Negative antagonists promote an inactive conformation of the $\beta_2$ -adrenergic receptor" Mol. Pharmacol. 45:390-394 (1994)
Schipani et al., "A constitutively active mutant PTH-PTHrP receptor in Jansen-type metaphyseal chondrodysplasia" Science 268:98-100 (1995)
Shenker et al., "A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty" <i>Nature</i> 365:652-654 (1993)
Showell et al., "High-affinity and potent, water-soluble 5-amino-1,4-benzodiazepine CCK <sub>B</sub> /gastrin receptor antagonists containing a cationic solubilizing group" <i>J. Med. Chem.</i> 37:719-721 (1994)

EXAMINER	DATE CONSIDERED

			Sheet <u>6</u> of <u>6</u>	-
SUBSTITUTE FORM PTO-1449	U.S. DEPARTMENT OF COMMERCE	Attorney Docket No.	00398/512002	
(MODIFIED) PATENT	PATENT AND TRADEMARK OFFICE	Serial No.	09/966,871	<b>\$</b> _
		Applicant	Alan S. Kopin et al.	CA
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		Filing Date	September 28 2001	
		Group	Not Assigned	82 2
	IDS Filed	January 11, 2002	(0)	
(37 C.F.R. §1.98(b))		Customer No.	21559	6000
				1300
				_

Strader et al., "Structure and function of G protein-coupled receptors" Annu. Rev. Biochem. 63:101-132 (1994)
Strader et al., "A single amino acid substitution in the β-adrenergic receptor promotes partial agonist activity from antagonists" <i>J. Biol. Chem.</i> 264:16470-16477 (1989)
Strader et al., "The family of G-protein-coupled receptors" FASEB J. 9:745-754 (1995)
Straub et al., "Expression cloning of a cDNA encoding the mouse pituitary thyrotropin-releasing hormone receptor" <i>Proc. Natl. Acad. Sci USA</i> 87:9514-9518 (1990)
Sugg, "Non-peptide agonist ligands for CCK-A receptors" Abstract (1995)
Sung et al., "Rhodopsin mutations responsible for autosomal dominant retinitis pigmentosa" <i>J. Biol. Chem.</i> 268:26645-26649 (1993)
Sunthornthepvarakul et al., "Brief Report: Resistance to thyrotropin caused by mutations in the thyrotropin-receptor gene" N. Engl. J. Med. 332:155-160 (1995)
Surratt et al., "-μ opiate receptor" J. Biol. Chem. 269:20548-20553 (1994)
Tiberi et al., "High agonist-independent activity is a distinguishing feature of the dopamine D1B receptor subtype" J. Biol. Chem. 269:27925-27931 (1994)
Tseng et al., "Carboxyl-terminal domains determine internalization and recycling characteristics of bombesin receptor chimeras" <i>J. Biol. Chem.</i> 270:18858-18864 (1995)
Wang et al., "Constitutive µ opioid receptor activation as a regulatory mechanism underlying narcotic tolerance and dependence" <i>Life Sciences</i> 54:339-350 (1994)
Watson et al., "Receptor & ion channel nomenclature supplement" Trends Pharmacol. Sci. Supplement 16 (1995)
 Westphal, "Reciprocal binding properties of 5-hydroxytryptamine type 2C receptor agonists and inverse agonists" <i>Molec. Pharmacol.</i> 46:937-942 (1994)
Westphal, "Properties of constitutively active serotonin 2C receptors (G protein, inverse agonist)" Dissertations Abstracts Intl., Vanderbilt Univ. 56:(05-B)2578 (1995)
Wiertelak et al., "Cholecystokinin antianalgesia: safety cues abolish morphine analgesia" Science 256:830-833 (1992)
Yokota et al., "Delineation of structural domains involved in the subtype specificity of tachykinin receptors through chimeric formation of substance P/substance K receptor" <i>EMBO J.</i> 11:3585-3591 (1992)
Yano et al., "A sporadic case of male-limited precocious puberty has the same constitutively activating point mutation in luteinizing hormone/choriogonoadotropin receptor gene a familial cases" <i>J. Clinical Endocrinology &amp; Metabolism</i> 79:1818-1823 (1994)

EXAMINER	DATE CONSIDERED